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Is Sertraline Effective At Reducing The Symptoms Of Anxiety In Those Diagnosed With Generalized Anxiety Disorder (GAD)?

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Is Sertraline Effective At Reducing The Symptoms Of Anxiety In Those Diagnosed With Generalized Anxiety Disorder (GAD)?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not sertraline is effective at reducing the symptoms of anxiety in those diagnosed with generalized anxiety disorder (GAD).

STUDY DESIGN: This is a systematic review of three randomized control trials (RCTs) published between 2008 and 2015, all in the English language and published in peer-reviewed journals.

DATA SOURCES: Three randomized control trials that study the effects of sertraline for reduction of anxiety symptoms in patients with GAD, obtained using PubMed, CINAHL Plus and Academic Search Premier.

OUTCOMES MEASURED: The primary outcome measured in each study was patient-reported reduction in anxiety symptoms and improvement of quality of life. These outcomes were measured using several scales, including the Hamilton Rating Scale for Anxiety, the Pediatric Anxiety Rating Scale, the Children's Global Assessment Scale, The Clinical Global Impression-Improvement Scale, and the Clinical Global Impressions Severity Scale.

RESULTS: Cvjetkovic-Bosnjak et al. found sertraline to be equally effective as pregabalin for the treatment of GAD (*Eur Rev Med Pharmacol Sci* 2015: 19 (11), 2020-2024). Similarly, Mokhber et al. found sertraline to be equally effective to buspirone in treating GAD (*Psychiatry Clin Neurosci*: 64: 128-133. doi: 10.1111/j.1440-1819.2009.02055.x). Finally, Walkup et al. found that sertraline and cognitive behavioral therapy either in combination or as monotherapies are effective in treating GAD (*NEJM* 2008; 359 (26): 2753-2766. doi: 10.1056/NEJMoa0804633).

CONCLUSION: The results of this systematic review show that sertraline is effective in treating the symptoms of anxiety in patients with a diagnosis of generalized anxiety disorder. While the results from these studies were promising, additional research with larger, more diverse populations, standardized measurements of outcomes, increased time frame, and further examination of adverse drug reactions and cost-effectiveness are required to determine the true long-term benefit of sertraline as therapy for GAD.

KEY WORDS: sertraline, generalized anxiety disorder.

INTRODUCTION

Generalized anxiety disorder (GAD) is a chronic mental illness with a prevalence of 5-7% in the general population.[1] While the exact etiology of this illness is unknown, it is likely multifactorial, and has been linked to disrupted functional connectivity of the amygdala and its processing of fear. In addition to constant worry, the physiological effects of anxiety may include headache, paresthesias, fasciculations, vertigo, syncope, abdominal pain, nausea, vomiting or diarrhea, indigestion, dry mouth, shortness of breath, tachycardia, chest pain, palpitations, frequent urination, perspiration or excessive fatigue.[3] GAD leads to functional impairment and significantly reduced patient's quality of life.[1]

The economic burden of anxiety on the healthcare system is tremendous and cannot be ignored. Though there is not an exact estimate within the past few years, between 2009 and 2011 there were an estimated 1,247,000 ED visits for anxiety annually, representing 0.93% of all ED visits in the United States.[4] Additionally, it is estimated that between 2009 and 2010, the annual overall direct medical costs associated with anxiety disorders in the US was $1657.52 per person, or $33.71 billion in total.[5]

Many different methods have been used to treat GAD. According to the guidelines of the World Federation of Societies of Biological Psychiatry, first-line treatments for GAD are selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs), and pregabalin, an atypical anxiolytic.[1] Long-acting benzodiazepines such as diazepam are also recommended for the treatment of anxiety.[6] Psychotherapy like CBT is recommended mostly in combination with pharmacotherapy.[1] Despite the many options already available, few patients with GAD receive adequate treatment. In fact, according to a 2009

national representative survey of 3,032 respondents in the United States, guideline-concordant care was received by only 32.5% of people with GAD in the primary care sector.[7]

While the aforementioned methods of treatment have had efficacy in treating anxiety, they are not without drawbacks. For example, Gale and Millichamp found that various drug treatments, such as benzodiazepines, buspirone, hydroxyzine, antidepressants, and pregabalin may all reduce symptoms of anxiety in people with GAD, but they can have unpleasant adverse effects, and most trials have been short term.[8] Additionally, Gale and Millichamp found that benzodiazepines, while effective, increase the risk of dependence, sedation, and accidents, and can be harmful to neonates if used during pregnancy.[8] Furthermore, buspirone may be less effective in patients who have recently taken benzodiazepines.[8]

Sertraline is an SSRI that is already commonly used to treat other anxiety disorders. For example, treatment of panic disorder with sertraline results in a decrease in the number of panic attacks and an improved quality of life.[9] Additionally, sertraline is effective for the treatment of social phobia.[10] Though sertraline is generally not a first-line drug for the treatment of GAD, it may have benefits for patients with this condition as well, given its already-proven efficacy with other anxiety disorders. In this systematic review, the effectiveness of sertraline at reducing symptoms of anxiety in those diagnosed with GAD will be evaluated through three randomized control trials.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not sertraline is effective at reducing symptoms of anxiety in those diagnosed with generalized anxiety disorder.

METHODS

The population studied in this systematic review was obtained from three randomized control trials that included patients suffering from symptoms of anxiety with a clinical diagnosis of GAD. Oral sertraline was the intervention studied in comparison with other methods of treating anxiety including pharmacologic therapy with buspirone and pregabalin, CBT and combination therapy. The key words employed in the author's search for sources via PubMed, CINAHL Plus and Academic Search Premier included "sertraline" and "generalized anxiety." All articles chosen for this systematic review include outcomes that are patient-oriented (POEMs) and are relevant to the author's clinical question. Articles selected fit the inclusion criteria of randomized control trials published after 2008 with no other systematic review, meta-analysis or articles published in the Cochrane database regarding the same clinical question. Studies were excluded if they were published before 2008 and not of a primary research design. Key statistics include p-values, confidence intervals, mean change from baseline and standard deviation. Additional relevant statistics reported included numbers needed to treat (NNT), experimental event rate (EER), control event rate (CER), absolute risk reduction (ARR), relative risk (RR) and relative benefit increased (RBI).

Table 1: Demographics and Characteristics of Included Studies

Study	Type	# Pts.	Age (yrs.)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Cvjetjovic-Bosnjak[1] (2015)	Double Blind RCT	107	20-60	Any male or female patient aged 20-60 with a diagnosis of GAD and an HAMA total score >20	Pts. w/ comorbid mental disorders (depression, alcoholism, personality disorders, psychotic disorders or somatic dysfunction (DM, HTN, cardiomyopathy, thyroid dysfunction).	0	Sertraline with a mean dose of 150 mg/day x 4 weeks vs. Pregabalan with a mean dose of 225 mg/day x 4 weeks.
Mokhber[11] (2010)	Single Blind RCT	46	>60	Any male or female with a DSM-IV	Patients w/ severe depressive symptoms or grief reaction in the past	0	Oral sertraline 50-100 mg/day x 8 weeks

				diagnosis of GAD, age >60, HRSA score >/= 20 and GDS severity score </=10	6 months; patients w/ any clinically important medical disease or abnormality on PE (e.g. head trauma, thyroid issues, acute heart disease); pts. w/ other Axis I psychiatric disorders or cognitive disturbances; pts. who used other drugs with psychotropic effects within 4 weeks prior to the study.		increased gradually according to a fixed incremental schedule vs. Buspirone 10-15 mg/day x 8 weeks.
Walkup[12] (2008)	Double-Blind RCT	488	7-17	Children between the ages of 7 and 17 years with a primary diagnosis of separation anxiety, GAD or social phobia	Children w/ unstable medical conditions or who were refusing to attend school due to anxiety or were unresponsive to two trials of SSRIs; sexually active/ pregnant females not using birth control; children receiving psychoactive medications other than stable doses of stimulants w/ psychiatric diagnoses; children who were an acute risk to themselves or others.	46	Sertraline administered on a fixed-flexible schedule beginning with 25 mg/day and adjusted up to 200 mg/day by week 8 vs. 8 weeks of CBT alone vs. 8 weeks of CBT/Sertraline combined.

OUTCOMES MEASURED

In this review, three RCTs were employed, two double blinded and one single blinded, with the measured outcomes being patient oriented evidence that matters (POEMs). The primary POEM measured in this review was reduction in symptoms of anxiety. This was ascertained using interviews with patients and several different scales. Cvjetkovic et al[1] and Mokhber et al[11] used the Hamilton Rating Scale for Anxiety (HRSA). Walkup et al[12] used four different scales, including the Clinical Global Impression-Improvement Scale, the Pediatric Anxiety Rating Scale, the Clinical Global Impressions Severity Scale, and the Children's Global Assessment

Scale. Data was statistically measured via the patient's self-reported reduction in anxiety symptoms using the above scales and reported either in terms of whether or not patients responded positively to treatment or as a change in means over the course of the study, using p-values and confidence intervals to determine the clinical significance of the data.

RESULTS

To determine if the effect of sertraline on anxiety symptoms was advantageous the three articles being evaluated used p-values. Cvjetkovic[1] claimed statistical significance if the p-value was <0.05. Mokhber[11] and Walkup[12] claimed statistical significance with a p-value of <0.01. In Cvjetkovic-Bosnjak et al[1] 107 patients aged 20-60 at an outpatient psychiatric clinic were randomly assigned to 4 weeks of treatment with pregabalin or sertraline. A mean daily dose of 150 mg of sertraline and a mean daily dose of 225 mg of pregabalin was given.[1] Patients attended weekly visits with two different psychiatrists to assess the severity of their anxiety symptoms, and at the end of the four week regimen, the final effectiveness and side effects assessments were made by the same psychiatrist that did the baseline evaluations.[1] patients treated with sertraline had a 10.1-point reduction in their overall HRSA score after 4 weeks[1] (Table 2). Additionally, 96% of patients treated with sertraline showed ratings of very much improved.[1] This study found that the most frequently reported adverse event amongst those treated with sertraline was nausea (13%), but that the adverse events were short-lasting and of mild intensity.[1]

Table 2. Change in Hamilton Anxiety Scale scores in patients with generalized anxiety disorder treated 4 weeks with sertraline[α]

HRSA Scores	Baseline	Week 1	Week 3	Week 4
Sertraline	24.00 +1.2	23.50 + 0.9	14.70 + 1.0	13.90 + 0.2
Pregabalan	23.60 +2.6	18.10 + 2.2	15.20 + 1.3	14.20 + 0.7

[α] Data derived directly from Cvjetkovic-Bosnjak et al[1]

Mokhber et al. studied 46 patients aged >60 with a clinical diagnosis of GAD. There were 21 patients receiving a daily dose of 50-100 mg of sertraline and 25 patients receiving a daily dose of 10-15 mg of buspirone, and the dosages were gradually increased according to a fixed incremental schedule.[9] Efficacy of these two medications was assessed by a psychiatrist blind to the treatment after 2, 4, and 8 weeks.[9] In this study, the mean score on the Hamilton Rating Scale for Anxiety after 8 weeks also significantly decreased in the sertraline group.[11] For the purpose of this review, the focus will remain on week 4 as an endpoint. (Table 3). By week 4, there was a nearly 25% decrease in HRSA scores for patients treated with sertraline.[11] No clinically significant serious adverse events were observed during the study period, and no one withdrew from the study.[11]

Table 3: Mean HRSA scores for patients treated with sertraline and buspirone weeks 0-4[α]

HRSA Scores	Week 0	Week 2	Week 4
Sertraline	28.63 +/- 5.19	28.48 +/- 4.90	21.48 +/- 4.64
Buspirone	28.84 +/-5.15	18.96 +/- 5.81	15.60 +/- 5.45

[α] Data derived directly from Mokhber et al[11]

Finally, Walkup et al. conducted a two-phase multicenter RCT for 488 children and adolescents between the ages of 7 and 17 years with a clinical diagnosis of GAD. Phase 1 was a 12-week trial of short-term treatment comparing cognitive behavioral therapy, sertraline, and their combination with a placebo drug, and phase 2 was a 6 month open extension for patients who had a response in phase 1. In phase 1, which is the primary focus of this review, CBT involved fourteen 60 minute sessions, while pharmacotherapy involved 8 sessions of 30-60 minutes each in which subjects rated the severity of their anxiety symptoms.[12] Sertraline and a matching placebo were administered on a fixed-flexible schedule beginning with 25 mg/day and adjusted up to 200 mg/day by week 8.[12] Patients were monitored for a total of 12 weeks via interviews administered by independent evaluators who were unaware of study group assignments.[10] For the purpose of this review, week 4 will be the endpoint studied. This study

used several different scales to measure outcomes. The Clinical Global Impression Improvement Scale demonstrated whether or not patients had a positive response to therapy, with a score from 1-7 in which 1 indicated very much improved and 2 indicated much improved.[12] The study found that the percentages of children with a score < 3 at 4 weeks was 18.8% in the sertraline group, exceeding those with a response to CBT or placebo in the same time frame[12] (Table 4).

Table 4. Patients (%) with response to sertraline, placebo, CBT, and combination therapy on the Clinical Global Impression-Improvement Scale with score <3 through week 4 [α]

Clinical Global Impression Improvement Scale	Week 4 outcomes
% with response to sertraline	18.8
% with response to placebo	6.6
% with response to CBT	9.3
% with response to combination therapy	21.4

[α]Data derived directly from Walkup et al[12]

Scores on the Pediatric Anxiety Rating Scale range from 0-30, with scores higher than 13 consistent with moderate levels of anxiety and a diagnosis of an anxiety disorder.[12] By the end of 4 weeks, there was nearly 25% rate of improvement in the sertraline group[12] (Table 5). Scores on the Clinical Global Impressions Severity Scale and the Children's Global Assessment Scale demonstrated similar levels of efficacy for sertraline by week 4.[12]

Table 5: Change in Pediatric Anxiety Rating Scale in patients treated with 4 weeks of sertraline or placebo or CBT or combination therapy[α]

Pediatric Anxiety Rating Scale	Baseline	Week 4
Sertraline	18.8 +/- 3.9	14.2 +/- 4.0
Placebo	19.6 +/- 3.9	16.0 +/- 4.1
Cognitive behavioral therapy	18.9 +/- 3.9	16.0 +/- 3.9
Combination therapy	19.4 +/- 3.9	14.6 +/- 3.9

[α]Data derived directly from Walkup et al[12]

DISCUSSION

While these studies demonstrate the efficacy of sertraline at reducing symptoms of anxiety in those with a diagnosis of GAD, they were not without limitations. Cvjetkovic-Bisnjak et al. was a small single center study with a limited age group and excluded patients with many comorbidities, limiting the generalizability of the study.[1] Mokhber at al. primarily focused on GAD in the elderly population, and was again limited by its small sample size.[9] Additionally, the association between medical illness, cognitive impairment, depression and GAD in the elderly excluded several subjects, thus limiting the generalizability of the study.[11] Walkup et al. acknowledged that despite intense outreach, the sample did not include the most socioeconomically disadvantaged children.[12] Additionally, exclusion of children and teens with major depression and pervasive developmental disorders may have limited the generalizability of the results to these populations.[12]

A final limitation of all three studies are the scales used to measure the outcomes. As noted, several different scales of measurement were used to assess the severity of anxiety symptoms. While the scales used are helpful in obtaining statistics about the specific populations studied, a more conclusive result may be obtained if a universal scale was utilized. For example, the Clinical Useful Anxiety Outcome Scale is one example of a standardized scale that may be used. A standardized scale will strengthen the validity of future studies on this topic.

In terms of cost, sertraline appears to be an affordable option to treat GAD. In June, 2006, after the U.S patent for Zoloft expired, sertraline was introduced in generic form worldwide.[14] Panzarino and Nash found that among the established SSRIs, drug acquisition costs were lowest for sertraline and paroxetine, and both are available in extended dosage forms to reduce the need for multi-tablet therapy.[14] Similarly, Ifigenia et al. found sertraline to be the most cost-effective

drug for patients with GAD.[15] While sertraline is often recommended in combination with CBT, Creswell et al. found that while cognitive behavioral therapy is effective, it is expensive and trained therapists are scarce.[16] In light of this, sertraline may be a more cost-effective method of solo therapy for GAD for those who do not have access to an affordable and qualified therapist.

More attention should be given to the negative side effects and drug interactions of sertraline. In October of 2004, the FDA issued a black box warning for sertraline indicating that the use of the drug in adolescents may increase the risk of suicidal ideations and behaviors.[17] Additionally, when compared to other SSRIs, sertraline tends to be associated with a higher rate of psychiatric side effects and diarrhea.[18] If used during pregnancy, sertraline increases risk of preterm delivery, low birth weight and lower APGAR scores.[19] While sertraline may be effective for treating GAD, the side effects cannot be ignored and should be further examined to determine if the risks outweigh the benefits of this drug.

CONCLUSION

From these three studies, it can be concluded that sertraline is an effective therapy for reducing symptoms of anxiety in those diagnosed with GAD. In all three studies, a statistically significant decrease in symptom severity was achieved in patients who underwent a daily trial of sertraline. In order to further assess the efficacy of sertraline as solo therapy for GAD, it would be beneficial to complete further studies with larger and more diverse population. The long-term safety, tolerability, and efficacy of sertraline should be further investigated, but there is benefit to short-term use of sertraline for reduction of anxiety symptoms in those with GAD.

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